In response to the Examiner's comments regarding the utility of the claimed invention, made during the February 6, 2003 interview, Applicant submits the following.

The specification clearly discloses a number of utilities for the claimed arrays of claims 1-13. The claimed arrays can be used to define a pattern of gene expression representative of an entire cell, tissue or organism enabling an expression profile to be created for that cell, tissue or organism in both healthy and pathological states (see p.1 and 8). At p. 8, lines 5-9, it is stated, "In still a further embodiment of an invention, an expression profile is generated comprising data related to the expression of a gene or group of genes in a biological system (e.g., a cell, group of cells, tissue, group of tissues, organ, or organism), in healthy and pathological states (where the biological system is subject to genetic alterations and/or environmental disturbances) using the arrays of the invention."

The claimed arrays of the invention are also useful for determining the expression profile of a previously unknown or uncharacterized gene or the expression profile of a known gene. (see p. 7 and 8). By determining whether any expressed target nucleic acid sequence within a sample hybridizes to the array, data relating to the expression of the target nucleic acid sequence in the sample is obtained (see p. 7).

In addition, the claimed arrays can be used to create expression profiles of two or more genes. These profiles can then be compared to each other and used to identify interactions between genes (see p. 8).

The claimed arrays can also be used to assess the biological relevance of a previously unknown or uncharacterized gene. It is stated at p. 8, lines 9-11, "In another embodiment, the biological relevance of a previously unknown or uncharacterized gene is determined by determining the expression profile of this gene in a biological system."

In the sections entitled "Method of Using cDNA Arrays For Gene Expression Monitoring" and "Gene Discovery Using cDNA Arrays" (p. 26- 36) details of how to use the claimed arrays to

1) Analyze expression of one or more genes;

2) Generate an expression profile for a gene or group of genes;

3) Monitor effects of a particular drug or set of drugs on gene expression;

4) Create an expression profile for a given pathology;

5) Determine the biological relevance of a previously unknown or uncharacterized gene

are provided.

In view of all of the above, Applicant submits that the invention as claimed clearly meets the legal requirements for utility under 35 U.S.C. § 101.

In response to the Examiner's suggestion during the February 6, 2003 Examiner interview that the pending claims of the instant application may not be novel in view of U.S. 5,858,656 (Deugau et al.) Applicant submits the following.

Deugau et al. relates to novel indexing linker molecules. It is stated at column 6, lines 37-51,

> "This invention provides novel indexing linker molecules which include a double stranded oligonucleotide with a first end having a protruding single strand of 3, 4, or 5 nucleotides, and a second end having a protruding single strand of any number of nucleotides including zero, characterized in that neither end, when paired with a complementary nucleotide cohesive end, will function as a restriction endonuclease recognition site.
>
> This invention further provides a set of indexing linker molecules each of which includes an oligonucleotide with a first end having a protruding single strand of 3 or more nucleotides, and a second end having a protruding single strand containing any number of nucleotides including zero wherein the sequences of the protruding single strands of the first end of members of the set are different."

It is also stated at column 10, lines 39-46 of Deugau et al, "Isolation of subsets or classes of nucleic acid fragments having a specific cohesive end can be accomplished by using one or more indexing linkers attached to a insoluble support. Preferably, a panel of indexing linkers its

attached to spatially segregated solid phase substrates which can be prepared by known procedures such as that, as described by S. S. Ghosn and G. F. Musso (1987) Nucl. Acids Res. 15:5353-5372)."

Applicants submit that for a determination of anticipation to be proper, the prior art reference must disclose each and every limitation of the claim. *Atlas Powder Company et al. v. IRECO, Incorporated et al.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

Claim 1 and dependent claims 3-13 claim "An array comprising a plurality of nucleic acid members, each member having a unique position and stably associated with a solid substrate, wherein each nucleic acid member comprises a non-coding sequence present in a 3'-end of an RNA transcript, and wherein each of said nucleic acid members is less than 600 nucleotides."

Claim 2 and dependent claims 3-4 and 7-8 and 10-13 claim "An array comprising a plurality of nucleic acid members, each member having a unique position and stably associated with a solid substrate, wherein each nucleic acid member comprises a non-coding sequence present in a 5' end of an RNA transcript, and wherein each of said nucleic acid members is less than 1000 nucleotides."

Applicant submits that Deugau et al. do not a teach nucleic acid member comprising a non-coding sequence present in a 3'-end of an RNA transcript, and wherein each of said nucleic acid members is less than 600 nucleotides; or a nucleic acid member comprising a non-coding sequence present in a 5' end of an RNA transcript, and wherein each of said nucleic acid members is less than 1000 nucleotides, as claimed in claims 1-13 of the instant application.

Applicant also submits that Deugau et al. do not teach "an array comprising a plurality of nucleic acid members, each member having a unique position and stably associated with a solid substrate, wherein each nucleic acid member comprises a non-coding sequence present in a 3'-end of an RNA transcript, and wherein each of said nucleic acid members is less than 600

nucleotides" or "an array comprising a plurality of nucleic acid members, each member having a unique position and stably associated with a solid substrate, wherein each nucleic acid member comprises a non-coding sequence present in a 5' end of an RNA transcript, and wherein each of said nucleic acid members is less than 1000 nucleotides", as claimed in claims 1-13 of the instant application.

In view of all of the above, Applicant submits that the invention as claimed is novel in view of Deugau et al.

Applicant has attached corrected drawings in response to the Notice of Draftsperson's Patent Drawing Review.

Pending claims

Claims 1-13 are pending. No new matter is added by this response.

Rejection of Claims 1-13 Under 35 U.S.C. §112, First Paragraph

Claims 1-13 remain rejected under 35 U.S.C. §112, first paragraph due to alleged lack of enablement.

The Examiner asserts, "[a]s presently worded, the claims have sufficient breadth of scope to encompass arrays of oligonucleotides that can be virtually any length, up to 599 nucleotides in length...The aspect of one of skill in the art being able to effectively produce pure populations of oligonucleotides of lengths up to 599 nucleotides in length is critical to enabling the making and use of the claimed invention." The Examiner cites Jones (U.S. Patent 5,858,671) as evidence of the difficulty in synthesizing an oligonucleotide that is 599 nucleotides in length.

Applicant respectfully disagrees.

Claims 1 and 2, and dependent claims 3-13 claim an "array comprising a plurality of **nucleic acid members**".

"Nucleic acid member" is defined at page 10, lines 29-31, as "either a single stranded or

double stranded nucleic acid which comprises a noncoding sequence present at either the 3'-end or the 5'-end of an RNA transcript."

Applicant submits that it is well known in the art that an oligonucleotide is a single stranded nucleic acid.

Claims 1-13 therefore encompass, but are not limited to an array comprising a plurality of oligonucleotides.

Applicant submits that methods of preparing pure populations of nucleic acid members that are up to 599 nucleotides in length, as claimed in claim 1 or up to 999 nucleotides in length, as claimed in claim 2, are well known in the art and are described in the instant application. Such nucleic acid members can clearly be produced without undue experimentation according to art accepted methods known in the art and described in the instant specification.

The specification teaches at p. 18, lines 19-21, production of a cDNA array by selecting cDNA sequences from a population of cDNA sequences, for example, a cDNA clone library, a population of reverse transcription products, or a population of RNA amplification products. One of skill in the art would accept that a nucleic acid member up to 999 nucleotides in length could be isolated from any of these populations using methods known in the art, including PCR.

Claims 1-13 are also rejected because the Examiner has interpreted these claims to encompass the limitations of claim 8. The Examiner states, "[i]n view of an independent claim encompassing all of the limitations of any of its dependent claim, claims 1-13 have been interpreted as encompassing non-known/not publicly available sequences. That is, claims 1-13 have been interpreted to encompass "non-known/not publicly available sequences."

Claim 8 claims "the array of claim 1 or 2, wherein at least 2% of the nucleic acid members on the array comprise sequences which are not included within a public database.

Applicant submits that Applicant knows of no basis in the law for interpreting claims 1-7 and 9-13 to encompass the limitations of claim 8. According to the doctrine of claim differentiation, "each claim in a patent is presumptively different in scope." "Claim differentiation...is clearly

applicable when there is a dispute over whether a limitation found in a dependent claim should be read into an independent claim." (*Wenger Manufacturing, Inc. v. Coating Machinery Systems, Inc.*, 239 F.3d 1225, pp (Fed Cir. 2001)).

"This doctrine [claim differentiation], which is ultimately based on the common sense notion that different words or phrases used in separate claims are presumed to indicate that the claims have different meanings and scope..." (*Karlin Tech., Inc., v. Surgical Dynamics, Inc.*, 177 F3d 968, pp, (Fed. Cir. 1999))

"The doctrine of claim differentiation provides that if a limitation is to be read into a claim, and if this added limitation already appears in another claim, then the additional words of limitation may not be used in the broader claim." (*Johnson Electric North America Inc. v. Mabuchi Motor America Corp.*, 77 F.Supp.2d 446, 454, n.9 (S.D.N.Y. 1999) (citing Treatise)

In view of the above, Applicant respectfully submits that there is no legal basis for reading the limitations of dependent claim 8 into each of claim 1-7 and 9-13.

Applicant also submits that claim 8 relates to an array comprising a plurality of nucleic acid members and does not relate to a nucleic acid or a plurality of nucleic acid members. The array of claims 1-13 is adequately described with regard to its properties (see pp. 12-18). Claims 1-13 are directed to an array comprising a plurality of nucleic acids, each of which has a unique position and is stably associated with a solid substrate. The array of claim 8 is also adequately described in the specification and is definite. Applicant submits further that one of skill in the art can easily identify an array of claim 1 or 2, wherein at least 2% of the nucleic acid members on the array comprise sequences which are not included within a public database, as claimed in dependent claim 8.

The Examiner states, "[I]n the present case [in comparison to Fiers, 984 F. 2d at 1171, 25 USPQ2d at 1606] the public is left with even less of a written description of the claimed nucleic acids...While applicant has articulated that one needs to practice a method so to determine if the

sequence is in a public database, such speaks to a result that one may achieve if they made the invention. That is different from actually providing a description of the invention. It is further noted that if the sequence is unknown to all, the specification has not provided an adequate description of the nucleic acids such that one of skill would recognize the sequence as comprising a non-coding nucleotide sequence present in the 3'-end of an RNA transcript."

Applicant submits that the invention as claimed in claims 1-13 is an array comprising a plurality of nucleic acid members and not the nucleic acid members themselves.

Applicant has clearly described the claimed array of claim 8. As stated in Applicant's response filed on October 31, 2001, in response to the June 20, 2001 Office Action, the specification defines a sequence not included in a public database and teaches how to identify a sequence not in a public database.

Applicant submits that an "unknown sequence" is described in the specification at p. 12, lines 1-12 as "a sequence not included in a public nucleic acid sequence database at the time the array was generated, either as a complete gene sequence, a partial gene sequence, a cDNA, or an expressed sequence tag (EST)."

Further, the specification teaches how to identify an unknown sequence. It is stated in the specification at p. 4, lines 20-25, "[i]n a further embodiment of the invention, the sequence information obtained from at least a portion of the 3'-end of the cDNA is compared to sequence information in a public database, and the cDNA is identified as a known sequence if there is substantial identity between the sequence of at least a portion of the 3'-end and a sequence in the database. If there is no substantial identity, the cDNA is identified as an unknown sequence, and sequence information relating to the cDNA is stored within the memory of a computer or a computer program product."

The specification clearly defines "substantial identity", as it refers to a sequence, at p. 21, lines 5-16 as follows.

"The term 'substantial sequence identity' in the context of two or more nucleic acid sequences refers to one or more sequences or subsequences that have at least 95% percent identity over a comparison window consisting of a specified number of nucleotides after having

been compared and aligned for maximum correspondence using a sequence comparison algorithm, or, alternatively by manual alignment and visual inspection. In one embodiment, a sequence having substantial sequence identity is a sequence which has at least 95% nucleotide sequence identity to a sequence in the database (a reference sequence) when aligned for maximum correspondence over a comparison window of 100 contiguous nucleotides, and preferably, 50-600 nucleotides. In a further embodiment of the invention, the sequence has at least 97% identity to the reference sequence when aligned for maximum correspondence over 200 nucleotides. Preferably, the sequence has 100% identity to the reference sequence when aligned for maximum correspondence over 200 nucleotides."

The specification teaches six methods of aligning sequences for comparison at p. 21, lines 18-28. The specification also teaches search tools for performing sequence alignments at p. 22, as well as a clustering algorithm for classifying sequences as known or unknown, at p. 23. Figure 2 of the instant application presents a diagram of a method for classifying sequences as known or unknown.

Applicant submits that as of the filing date of the instant application, Applicant was clearly in possession of the claimed invention, and have put the public in possession of the claimed invention. That is, applicant has clearly described "an array comprising a plurality of nucleic acid members, each member having a unique position and stably associated with a solid substrate, wherein each nucleic acid member comprises a non-coding sequence present in a 3'-end of an RNA transcript, and wherein each of said nucleic acid members is less than 600 nucleotides, as claimed in claim 1 and dependent claims 3-7 and 9-13. Applicant has also clearly described "an array comprising a plurality of nucleic acid members, each member having a unique position and stably associated with a solid substrate, wherein each nucleic acid member comprises a non-coding sequence present in a 5' end of an RNA transcript, and wherein each of said nucleic acid members is less than 1000 nucleotides", as claimed in claim 2 and dependent claims 3, 7 and 10-13. Applicant has also described how to identify a nucleic acid member comprising an unknown sequence and thus have adequately described the array of claim 8 wherein "at least 2% of the nucleic acid members on the array comprise sequences which are not

included in a public database." Thus, in view of all of the above, Applicant was clearly in possession of the claimed invention of the instant application as of the filing date and have fulfilled the requirements of 35 U.S.C. § 112, first paragraph.

In view of all of the above, Applicant respectfully requests that the above §112, first paragraph rejections be reconsidered and withdrawn.

Rejection of Claim 4 Under 35 U.S.C. §112, second paragraph

Claim 4 is rejected under 35 U.S.C. § 112, second paragraph for alleged indefiniteness.

The Examiner states, "[t]he term primarily is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention."

Claim 4 has been amended to claim "the array of claim 1 or 2, wherein each said nucleic acid member comprises substantially noncoding sequences."

It is stated in the specification at page 10, lines 9-11, "[a]s used herein, a nucleic acid sequence which 'contains substantially noncoding sequences' refers to a nucleic acid sequence which encodes less than 50% of a full length protein."

In view of all of the above, Applicant respectfully requests withdrawal of the 35 U.S.C. 112, second paragraph rejection of claim 4.

CONCLUSION

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Respectfully submitted,

Date: February 10, 2003

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MARKED UP CLAIMS

4. (Twice Amended) The array of claim 1 or 2, wherein each said nucleic acid member comprises [primarily] substantially noncoding sequences.